

Relationship Between the Amount of Rice Oil Ingested by Patients with Yusho and Their Subjective Symptoms

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The goal of this study was to clarify the subjective symptoms closely related to Yusho by examining the relationship between the amount of PCB-contaminated rice oil ingested by patients and the subjective symptoms recorded on their questionnaires. The amount of PCB-contaminated rice oil consumed by the patients was obtained by interviewing the housewife in each Yusho family. Individual consumption of the oil was estimated by taking into account age, sex and the number of meals at home. In 1970, 46 patients were available for analysis, and in 1971, 33 patients were available.

Among 12 subjective symptoms studied, numbness of the limbs, coughing, expectoration, and the sensation of "elevated" teeth were considered to show a dose-response relationship, which suggests that these subjective symptoms are closely related to Yusho. Consistent high rates of complaints of general fatigue and eye discharge were considered possibly to be connected with Yusho, although no dose-response relationships have been determined. Other subjective symptoms, such as fever, headache, dizziness, abdominal pain, swelling in the joints, changes in menstruation, and loss of hair failed to show consistent dose-response relationships. It should be noted, however, that for these symptoms which failed to show dose-response relationships, it is impossible to deny a causal relationship.

Introduction

In 1968, over one thousand persons in the western part of Japan suffered from polychlorinated biphenyl (PCB) poisoning as a result of ingestion of a commercial brand of rice oil contaminated with the chemicals (1,2). This disease, called Yusho (oil disease), was characterized by such symptoms as follicular accentuation, acneform eruptions, pigmentation of the skin and nails, and hypersecretion of the Meibomian gland. Besides these clinical signs, the patients had various subjective symptoms which are also commonly observed in other diseases. Among the complaints, seven symptoms were listed as conditions connected to Yusho in the diagnostic criteria revised in 1976, based on clinical observation (3): general fatigue, heavy headedness or headache, paraesthesia of the limbs, eye discharge, cough and expectoration, inconstant abdominal pain, and changes in menstrual cycles.

The present study was made to determine which of these subjective symptoms are closely related to Yusho. For this purpose the patients group was compared with healthy controls. However, since these symptoms could be highly subjective, it would be expected that complaints of the patient group might be apparently more prevalent than those of the healthy controls. In order to avoid such bias, the dose-response relationship between such symptoms and the amount of contaminated oil ingested by the patients was studied.

Subjects and Methods

The amount of rice oil ingested by patients with Yusho has been estimated and reported (4). In 1969 and 1970, housewives of the families in which Yusho occurred were interviewed to determine the amount of contaminated rice oil purchased, the amount not used, the duration of the rice oil consumption at home and the number of meals eaten by each patient at home per week during the period the contaminated rice oil was being used.

In order to estimate individual rice oil consumption, the total amount of rice oil used by each household was proportionally distributed to the family members according to the frequency with which each member of the household ate meals at home and the person's sex

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and age. The details of the method of estimation have been described elsewhere (5). This estimation was made only on the patients who had consumed canned rice oil produced or shipped on February 5 and 6, 1968. These patients were classified into three groups according to their rice oil consumption: those who had consumed less than 500 mL (small amount group); those who had consumed 500–999 mL (moderate amount group); those who have consumed 1000 mL or more (large amount group). Individual rice oil consumption per kilogram body weight per day was not used, because it had been demonstrated in another study (6) that a definite dose–response relationship was observed between the total rice oil consumption and blood PCB level of patients but not between rice oil consumption per body weight per day and blood PCB level.

An annual physical examination has been carried out for patients with Yusho at a Yusho clinic at Kyushu University since the outbreak. Since 1970, self-administered questionnaires on 12 subjective symptoms have been distributed and completed by the patients attending the Yusho clinic at the annual examination. In addition, 11 subjective and objective symptoms were evaluated at the Yusho clinic by physicians and recorded on examination sheets.

These two different sets of data for subjective symptoms as assessed, by patients and by physicians, were analyzed independently to ascertain the dose–response relationship, if any, for each subjective symptom. In the present study, analysis was carried out only on the patients for whom both individual rice oil consumption and subjective symptoms were known.

Based on these data, the relationship between rice oil dose and subjective symptoms was analyzed by 2×3 table. Sex and age are confounding factors which can affect the dose–response relationship between subjective

sive symptoms and the rice oil dose. To minimize the effect of these factors, stratification was made by sex and age, and Mantel's extension method and the Mantel-Haenszel method were adopted to get a summary χ^2 trend from the stratified tables (7,8).

Results

Individual rice oil consumption was estimated for 141 patients with Yusho as reported previously (5). Of these, 53 patients whose consumption of contaminated rice oil was determined had received an annual clinical examination in 1970, and 37 had been examined in 1971. Of these patients, 46 (86.8%) and 33 (89.2%) patients had responded to the self-administered questionnaires for subjective symptoms in 1970 and 1971, respectively. The responses obtained in 1970 from the 46 patients showed that 11 had consumed small amounts, 22 moderate amounts and 13 large amounts of contaminated oil; the responses from the 33 patients in 1971 were distributed 8, 17 and 8, in the respective consumption groups.

Proportions of patients complaining of each subjective symptom are presented in Table 1. In 1970, proportions of complaints of headache, dizziness, feeling of elevated teeth, numbness of the limbs, and expectoration increased with increase in the amount of rice oil ingested. Among these trends, only those for the last two symptoms were statistically significant.

In the group surveyed in 1971, headache, abdominal pain, numbness of the limbs, cough, expectoration, and feeling of elevated teeth tended to have a dose–response relationship. Among these subjective symptoms, only cough was shown to be statistically significant in the trend.

Besides these facts, fairly frequent complaints of fatigue and eye discharge were also observed at every

Table 1. Relationship between total amount of PCB-contaminated rice oil consumed and subjective symptoms cited by patients.

Symptom	1970					1971				
	% of patients with symptom				Critical level for trend ^d	% of patients with symptom				Critical level for trend ^d
	No.	Small dose ^a	Moderate dose ^b	Large dose ^c		No.	Small dose ^a	Moderate dose ^b	Large dose ^c	
Fatigue	46	81.8	86.4	84.6	1.00	33	75.0	100.0	87.5	0.58
Fever	46	0.0	18.2	7.7	0.61	31	0.0	6.3	0.0	0.85
Headache	45	54.6	68.2	91.7	0.07	33	50.0	58.8	62.5	0.68
Dizziness	46	45.5	54.6	61.5	0.66	30	50.0	40.0	28.6	0.38
Abdominal pain	46	45.5	72.7	46.2	1.00	30	25.0	41.2	50.0	0.25
Numbness of limbs	45	27.3	57.1	76.9	0.05	33	37.5	47.1	62.5	0.29
Cough	46	36.4	40.9	38.5	0.70	33	12.5	41.2	62.5	0.05
Expectoration	46	45.5	68.2	92.3	0.02	33	25.0	58.8	62.5	0.20
Irregular menstruation	15	33.3	66.7	33.3	0.79	12	66.7	25.0	60.0	0.86
Feeling of elevated teeth	46	36.4	45.5	69.2	0.08	33	25.0	52.9	62.5	0.22
Loss of hair	46	36.4	27.3	23.1	0.32	30	25.0	56.3	33.3	0.90
Eye discharge	46	100.0	100.0	100.0	1.00	33	100.0	100.0	100.0	1.00

^aTotal oil consumption = 0–499 mL.

^bTotal oil consumption = 500–999 mL.

^cTotal oil consumption = >1000 mL.

^dCritical level (p) is based on χ^2 trend using Mantel's extension and the Mantel-Haenszel method.

dose level, both in 1970 and 1971, although no dose-response relationship for these symptoms was observed.

In order to confirm the above results obtained from the self-administered questionnaires, information collected from records of the annual physical examination was analyzed in the same manner. The information had been obtained on 51 (96.2%) of the 53 patients and on all of the 37 patients who had the clinical examinations in 1970 and 1971 (Table 2). In 1970, fever, peripheral nerve symptoms and abnormalities of teeth increased with rice oil consumption at < 5% level of significance. The same tendency was shown in symptoms of the central nervous system, cough, expectoration, although no significant trend was revealed.

The 1971 data showed a significant dose-related trend only in expectoration, at 2% of critical level. Cough and abnormalities of teeth seemed to have the same tendency without statistical significance.

In 1970 and 1971, high prevalence rates of general fatigue and eye discharge were recorded regardless of the amount of the rice oil ingested (Table 2). Considering the results obtained from the questionnaires and the

examination records, numbness of limbs, cough, expectoration, and teeth symptoms may have a dose-response relationship.

Discussion

In order to specify subjective symptoms that closely relate to Yusho, proportions of each complaint by patients should be compared with those by healthy controls. However, it would be very difficult to find a suitable healthy control group which is comparable with the patients. Fortunately, it was found that periodic health checkups for clerical workers at a factory required them to fill out a self-administered questionnaire similar to the one used in this study. In the questionnaire in 1977, 7 of the 12 subjective symptoms were comparable: fatigue, fever, headache, dizziness, abdominal pain, numbness of the limbs, and expectoration. All the symptoms but fever were more frequently cited by Yusho patients aged 15 to 49 than by the healthy workers aged 20 to 49 with statistical significance, as shown in Table 3. It is probable,

Table 2. Relationship between total amount of PCB-contaminated rice oil consumed and symptoms or signs recorded by physicians.

Symptoms and signs	No.	1970				No.	1971				Critical level for trend ^d
		% of patients with complaint			% of patients with complaint						
		Small dose ^a	Moderate dose ^b	Large dose ^c	Small dose ^a		Moderate dose ^b	Large dose ^c			
General fatigue	51	83.3	90.9	82.4	0.58	37	75.0	100.0	91.7	0.54	
Fever	50	0.0	14.3	17.6	0.04	36	0.0	11.8	9.1	0.43	
Symptoms of central nervous system	50	50.0	71.4	76.5	0.25	37	37.5	58.8	41.7	0.82	
Symptoms of digestive system	50	45.5	72.7	47.1	1.00	37	25.0	41.2	33.3	0.77	
Symptoms of peripheral nervous system	50	25.0	52.4	82.4	0.01	37	50.0	47.1	66.7	0.34	
Cough	51	33.3	45.5	52.9	0.26	37	12.5	41.2	50.0	0.10	
Expectoration	51	50.0	68.2	82.4	0.14	37	25.0	58.8	83.3	0.02	
Abnormality in menstruation	14	33.3	40.0	16.7	0.53	13	50.0	40.0	33.3	0.66	
Abnormality in teeth	51	33.3	45.5	70.6	0.03	37	25.0	52.9	66.7	0.11	
Loss of hair	51	25.0	22.7	17.6	0.58	36	25.0	58.8	18.2	0.41	
Eye discharge	51	100.0	95.5	100.0	1.0	37	100.0	100.0	100.0	1.00	

^a Total oil consumption = 0 - 499 mL.

^b Total oil consumption = 500 - 999 mL.

^c Total oil consumption > 1000 mL.

^d Critical level (*p*) is based on χ^2 trend using Mantel's extension and the Mantel-Haenszel Method.

Table 3. Complaints of subjective symptoms: Yusho patients vs. healthy controls.

Symptoms	Male					Female				
	13 Yusho patients with complaints		3250 healthy controls with complaints		Level of significance <i>p</i>	16 Yusho patients with complaints		484 healthy controls with complaints		Levels of significance <i>p</i>
	No.	%	No.	%		No.	%	No.	%	
Fatigue	11	84.6	332	10.2	< 0.01	14	87.5	42	8.7	< 0.01
Fever	0	0.0	68	2.1	NS	3	18.8	8	1.7	< 0.01
Headache	8	61.5	184	5.7	< 0.01	13	86.7	52	10.7	< 0.01
Dizziness	7	53.8	174	5.4	< 0.01	10	62.5	47	9.7	< 0.01
Abdominal pain	8	61.5	290	8.9	< 0.01	8	50.0	45	9.3	< 0.01
Numbness of limbs	10	76.9	44	1.4	< 0.01	8	50.0	12	2.5	< 0.01
Expectoration	9	69.2	240	7.4	< 0.01	11	68.8	17	3.5	< 0.01

therefore, that these six symptoms are related to Yusho. However, since these symptoms are quite subjective, it is extremely difficult to draw any conclusion from this kind of simple comparison.

When a dose-response relationship is examined, it is less likely that the patients' awareness of their subjective symptoms is systematically affected by the amount of rice oil ingested, because patients did not know the exact amount of the oil ingested. Therefore, the possible bias, if any, in the present study must be small.

In the results obtained, numbness of the limbs, cough, expectoration and tooth symptoms showed a dose-response relationship in 1970 and 1971, but in 1976 this relationship disappeared. It may be that the dose-response relationship became less distinct with the lapse of time.

A question can be raised as to whether or not the subjective symptoms showing a dose-response relationship are compatible with the specific clinical signs of Yusho. Kuroiwa reported in 1969 that 10 of 23 patients with Yusho showed symptoms and signs of sensory neuropathy such as numbness, pain and hypoaesthesia of the limbs (9). It was also reported that the sensory nerve conduction velocity was reduced in about half of the 21 patients examined (10). Thus, numbness of the limbs as a subjective symptoms can be considered to relate to Yusho.

Cough and expectoration could be also associated with Yusho, because it was reported that clinical findings similar to chronic bronchitis were observed among half of the patients examined (11,12) and that respiratory symptoms correlated well with the concentration of PCB in the blood (13). The sensation of "elevated" teeth could be due to inflammation of the gingiva. However, abnormalities in teeth or gingiva, except pigmentation, were not described well.

If a subjective symptom is cited by all of the patients, a dose-response relationship cannot be shown in the data. The dose-response relationship in eye discharge would be such a case, because clinically, eye discharge was viewed to be one of the typical clinical features of Yusho (3,14). A dose-response relationship was also shown between blood PCB level and ocular signs (15). Almost all patients with Yusho complained of fatigue. Although the mechanism for the symptoms of Yusho has not been clarified, it should be considered that this symptom is related to Yusho.

Conclusion

Among 12 subjective symptoms studied, numbness of the limbs, cough, expectoration, and sensation of "elevated" teeth were considered to show a relationship to dose, which suggests that the subjective symptoms are closely related to Yusho. Consistent high rates of complaints of general fatigue and eye discharge were considered to be closely connected with Yusho, although no dose-response relationship was determined. Other subjective symptoms such as fever, headache,

dizziness, abdominal pain, swelling of the joints, changes in menstrual cycles, and loss of hair did not show any consistent dose-response relationship. It should be noted, however, that it is impossible to deny a causal relationship for these symptoms which failed to show a dose-response relationship.

The result stated above is only a clue to stimulate further investigations from the clinical and etiological points of view in order to clarify the relationship between the symptoms and Yusho.

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